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Step 2/3 Rapid Review Series (118)

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- **Dr Mohammed Zaki**
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Scleroderma and Esophageal Complications

So what if they give you a question about a patient, and they tell you that this patient—the skin around their hands and their fingers—looks very tight. Around their forearm, it looks very tight. And you're told that this person has been having dysphagia for the past one month. And that the person's symptoms have not been well controlled with over-the-counter therapies. And then they ask, what's your most appropriate next best step in management?

So I would really hope that on your exams you're thinking of getting an EGD—getting an esophagogastroduodenoscopy. So this person probably has scleroderma, right? And we know that scleroderma can cause a lot of problems with the esophagus. Many of you probably know about CREST scleroderma. So what does CREST stand for? Well, the C stands for calcinosis. The R stands for Raynaud's phenomenon. The E stands for esophageal dysmotility. The S stands for sclerodactyly, and then the T stands for telangiectasias.

Now, the thing is, the NBME—they know that we live in an Anki generation, right? They literally know that all of you have memorized scleroderma, scleroderma, scleroderma. CREST, CREST, CREST. It's in many Anki decks out there. So what is the easiest way to see if people really understand what's going on? It's to just bring in an esophageal problem in a somewhat different light from what you're used to.

So, for example, what would this be like? Well, if you think about it, people that have scleroderma, right—they've literally fibrosed their esophagus, they've fibrosed many parts of their GI tract. So that fibrosis can actually cause incompetence of the lower esophageal sphincter. And these people—can have significant GERD.

But let me ask you this: this significant GERD—what can it lead to? What kind of big long-term problem can it lead to that can also cause dysphagia? It can cause esophageal dysmotility that makes it hard for you to swallow. But one weird thing that you may see on your exams—believe it or not—is that these people may develop esophageal strictures. OK? They may absolutely, positively develop what? Esophageal strictures. This is actually something that many people do not keep in mind. On your tests, whenever you have chronic GERD, that can lead to the development of adhesions and strictures in your esophagus. And when you have those adhesions, when you have those strictures, it can make it hard for food to pass through.

So our friends at the NBME—they can literally give you a scleroderma question, and they intentionally omit information that relates to esophageal dysmotility or relates to GERD. And the right answer will end up being that the person has esophageal strictures. So it's just something I want you to keep at the back of your mind on exams. In fact, they can give you a question about a person that has scleroderma, and this person is losing weight, and this person is having dysphagia to solids, right? If you see that, again, you want to get that EGD because these people can absolutely get esophageal adenocarcinoma.

Again, see, let me tell you something. USMLEs these days—it's not like they've suddenly stopped testing the classic pathologies that they have always tested. No, they've not stopped. That's one thing people need to get into their brains. They have not stopped.

But one thing that they've started doing these days—it's almost like a counter against this pervasive Anki use and people just memorizing things without understanding—is that they create questions these days where it's the same classic pathologies they test, but they test it in an unusual population, right?

Like, for example, it's like giving Pneumocystis jirovecii to a person that does not have HIV. Everybody knows the association—interstitial pneumonia in HIV patients, Pneumocystis jirovecii—all of you know that. But how about giving Pneumocystis jirovecii to people that are on chronic steroids? How about giving Pneumocystis jirovecii to people that are on chemotherapy? How about giving Pneumocystis jirovecii to post-transplant patients that are on immunosuppression? These are all things they can do to you on an exam, right?

So don't think that Barrett's esophagus and esophageal adenocarcinoma will just be restricted to people that consume alcohol, people that are unhealthy and obese—although alcoholism probably raises your risk more for esophageal squamous cell cancer, right?

So just be careful that anything that causes incompetence of the lower esophageal sphincter, right? So say, for example, if you have scleroderma because you've fibrosed your esophagus—that can cause you to have Barrett's esophagus. That can cause you to have esophageal cancer.

You saw how I just discussed the dysphagia question in a person with scleroderma, and it was due to strictures, right? So you want to be careful about that on your exams. Please be careful about that on your exams.

Lower Esophageal Sphincter Hypotonia in Pregnancy

Another thing that can also cause incompetence of the lower esophageal sphincter—since we're talking about it, let's make the integration—although many times these people are not going to proceed with the Barrett's all the way to esophageal cancer because it's a temporary thing, it's pregnancy, right?

So they can give you a question about a pregnant woman. They will say that this lady—her last menstrual period was like 10 weeks ago—and that this patient has this sore sensation in her upper throat that is worsened by lying down, and it improves when she sits up. It improves over the course of the day, right? But it's worse at night, right? And they will say that omeprazole was administered, which significantly improved her symptoms.

And then they ask you: what is the most likely underlying mechanism behind this patient's presentation? Pick the answer that says "lower esophageal sphincter hypotonia," right? Or pick the answer that says "incompetence of the lower esophageal sphincter."

So you may wonder, Divine, what in the world are you talking about? How can a person have incompetence of the lower esophageal sphincter? How can they have hypotonia of the lower esophageal sphincter and be pregnant?

Well, the thing is, when you're pregnant, there's this amazing thing called the placenta, right? Now, one of the things that is produced in high quantity by the placenta is progesterone. Many people do not give progesterone credit for this, but progesterone is a very powerful smooth muscle relaxant. I'm going to say that again: progesterone is a very, very powerful smooth muscle relaxant.

So because progesterone is a powerful smooth muscle relaxant, it can actually relax your lower esophageal sphincter. And you can have a ton of reflux that can cause significant GERD. If any of you are listening to this podcast and you've ever been pregnant, you probably know that—gee, once pregnancy comes, amazing GERD just shows. And it's pretty remarkable—after you deliver your baby, you notice that within a few days or a few hours, that GERD just completely resolves. Why? Because the placenta is out.

If the placenta is out, let me tell you this: where is that source of progesterone? It's gone. That's why you notice many women that are pregnant are placed on PPI therapy—are placed on PPI therapy. Again, keep those integrations in mind, right?

Progesterone explains so many things you see in pregnancy—even like the reduction in blood pressure you see in pregnancy. Right? Think about it: if you're a smooth muscle relaxant, you're going to decrease the systemic vascular resistance. If you decrease the systemic vascular resistance, that's going to lower your diastolic blood pressure. It's going to lower your blood pressure, right?

Or think about it in pregnancy—you notice that, man, most times when you go for your prenatal visit—and again, all these things are USMLE questions, by the way—you're going for your prenatal visits, and you notice that they're always collecting a urine sample because you have a high UTI risk during pregnancy.

Well, why is that the case? The reason that's the case is because in pregnancy—in pregnancy, remember—what is one thing that happens? One thing that happens is that your ureters are lined with smooth muscle. If you relax the smooth muscle that lines your ureters, that is going to cause you to have ureteral dilation. If you have ureteral dilation, that's going to cause urinary stasis. And if you have urinary stasis, guess what can happen? That can increase your risk of developing UTIs, right?

Just think of like stationary fluid—that's a great nidus for bacteria to build up, right? And what's going to be the most common cause of UTIs? I hope you're saying, Divine, it's going to be E. coli. It's going to be E. coli, right? So make sure you know these things for your tests.

Capacity vs Durable Power of Attorney (DPOA)

Now, what if they give you a question about a patient, and they tell you that this patient has appointed a durable power of attorney. But this patient—yes, they've appointed a durable power of attorney—but the patient still has capacity. And who is going to make decisions for the patient? Is it going to be the patient or the DPOA, the durable power of attorney?

I hope you're saying that, Divine, the person that's going to make decisions for this patient is going to be the patient themselves. This is one thing that many people screw up on the USMLE exams. The fact that you have a durable power of attorney does not mean that you cannot make decisions for yourself.

I'm going to say that again: the fact that you have a durable power of attorney does not mean you cannot make decisions for yourself. You absolutely, positively can still make decisions for yourself.

What is the role of a durable power of attorney? The role of a durable power of attorney is to help you make decisions in the event that you become incapacitated.

But as long as you still use it—as long as you can still make decisions—you can absolutely, positively still make your own decisions. Even if the DPOA is in the picture, it doesn't mean anything. Again, your DPOA only comes into full view when you're in a situation where you are incapacitated—you've lost the ability to make decisions for yourself.

Hemolytic Uremic Syndrome (HUS) and Shigella

Alright, now what if they give you a question about a patient, and they tell you that this is a 14-year-old male, and for the past 5 days, he has been having bloody bowel movements, right? This person has been having nosebleeds, and they tell you that this child has ecchymosis of the skin.

And then they give you labs, and you notice that the child's platelet count is 12,000, and the creatinine is like 3.5, right? And then they say, what is the most likely underlying cause of this patient's presentation?

And then they put an answer that says Salmonella. They put an answer that says Shigella. They put an answer that says enterotoxigenic E. coli. They put an answer that says Giardia lamblia. And then they put an answer that says Entamoeba histolytica.

What answer should you pick? I would really hope you're picking the answer that says Shigella. I would really hope you're picking the answer that says Shigella.

So let's talk about this, right? So what does this child have? I would hope you're saying, Divine, it appears that this child has hemolytic uremic syndrome. I'm going to say that again—this child has what? Hemolytic uremic syndrome.

Now, I know some of you may be like, Divine, the answer you're picking makes no sense. Why are we not picking the E. coli answer? Well, this is where paying attention to your exam question is very helpful.

What E. coli did I mention? I mentioned enterotoxigenic E. coli, right? Remember, that's one of the most common causes of traveler's diarrhea, right? Enterotoxigenic E. coli. I did not say E. coli O157:H7. E. coli O157:H7 is the one that causes HUS—not ETEC. ETEC does not cause HUS.

But if you notice, I was very coy in putting an E. coli species as the answer because in the heat of an exam, when people are not focusing—when people are not reading—they can be misled and pick E. coli as an answer, instead of picking Shigella.

Make sure you're picking the right E. coli species. ETEC does not cause HUS on the exam. The thing that causes hemolytic uremic syndrome is enterohemorrhagic E. coli—E. coli O157:H7. That is the most common cause of HUS.

But since we did not see that specific E. coli species in this question, you need to go for the next best thing, which is Shigella, right?

And what tells us in this question that this person has hemolytic uremic syndrome? Well, we know this person has HUS because the person has bloody diarrhea, right? The person has thrombocytopenia. And instead of telling you directly that the platelet count is low, they give you clues—they tell you the person has nosebleeds, right? So bleeding—because they don't have good primary hemostasis.

The person has ecchymosis, petechiae, purpura on the skin. The thing is, sometimes with these questions, instead of giving you the low platelet count—because the low platelet count gives things away—they can give you antecedents of low platelets instead.

Like what? They can give you things like ecchymosis. They can give you things like petechiae. They can give you things like purpura on the skin. So just be mindful of that. And you see this person has acute renal failure as well, right? We see the person's creatinine is elevated.

So what are some follow-up questions you may see with this? Well, if you think about it, they can ask: what is the most likely finding on a peripheral blood smear in this patient? I really hope you're saying that—oh, Divine, I'm going to pick the answer that says schistocytes, right? Schistocytes. Remember, another name you may see for schistocytes on your exams is fragmented erythrocytes. OK? Fragmented erythrocytes.

Typically, you're going to see schistocytes on a blood smear when a person has something causing a MAHA. What do I mean by MAHA? MAHA means microangiopathic hemolytic anemia.

So typically, these people, right—they can have all these things. Sometimes they can have these von Willebrand factor multimers that are literally shearing the red blood cells in their bloodstream, right? That's what creates those schistocytes.

And I would really hope that you know the other causes of schistocytes on your exams, right? DIC, right? Disseminated intravascular coagulation. A person that has TTP—thrombotic thrombocytopenic purpura—that can cause schistocytes on your exams as well, right?

And then they can ask you: what is the most likely mechanism behind this patient's bloody bowel movement? Well, I hope you're picking the answer that talks about invasion of the intestinal mucosa. Invasion of the intestinal mucosa.

The thing is, whenever you see a bug that causes bloody diarrhea, it usually causes that problem by invading the intestinal mucosa, right?

So like, for example, if you think about it—Shigella. Shigella invades. What it does is that it's picked up by your immune system cells that we find around the terminal ileum. It's picked up by those cells. But the thing is, when it's picked up by those cells, it destroys those immune system cells, right?

And when you destroy those immune system cells, guess what's going to happen? The thing is, as it destroys, it then spreads into the other epithelial cells that line your GI tract, and it's going to cause those cells to die. And as those cells die and they slough off, you're going to have bloody diarrhea.

Shigella is like a special operations operative, like a special forces operative. It just needs like 10 organisms, and you're in deep trouble, right? You're literally in deep trouble.

And the thing is—since again, our friends at the USMLEs love to go after basic sciences these days—first things first, what are the immune system cells we find—or what's like the big component of the immune system—you'll find around the terminal ileum? I would really hope you're saying, Divine, we have those Peyer's patches.

Please do not ignore these basic science things. Do not think that, "Oh, I am done with the USMLE Step 1 examination. I do not have to worry about these things anymore." No—you could not be more mistaken.

On your exams, again—since Step 1 became pass/fail, and especially since last year—our friends at the NBME have become very good at shunting a lot of basic sciences to the USMLE Step 2 CK and Step 3 exams, right?

So again, don't forget your Peyer's patches that we find in the terminal ileum. Right—in the terminal ileum. And remember, the classic Shigella that they love to go after on the exams is Shigella sonnei. Shigella sonnei—S-O-N-N-E-I. Shigella sonnei, right?

So keep that in mind.

And this child that has HUS—how are we going to treat this child that has HUS? We're going to treat this child with supportive care. OK? Supportive care.

They will try to trick you on your exams into treating the Shigella by giving antibiotics. That could not be a worse decision that you could take for this child. The problem with that is that it's the toxin—the Shiga toxin—that is causing the problem. So if you give antibiotics, you're going to kill more bugs. If you kill more bugs, you release more toxin. If you release more toxin, you will explode the child's kidneys. You will absolutely destroy this child.

So don't do that, right? That's not a smart thing to do. OK? Please—that is not a smart thing to do on your exam.

Many people ignore how powerful bacterial toxins can be—in real life, but also on the USMLE exams, right?

High-Yield Toxin Mechanisms

In fact, since I'm talking about toxins, let's make some toxin integrations, right? Let's make some toxin integrations that our friends at the NBME love to throw on exams.

Number one—right—we've kind of talked about the Shiga toxin, right?

Well, what's another toxin you may see on your exams? Well, think about a person having toxic shock syndrome, right? Toxic shock syndrome.

Toxic shock syndrome is usually going to be caused by toxins, right? It's caused by the release of exotoxins, right? Those exotoxins are released and those things cause you significant pain, significant trouble.

This is why, when a person has toxic shock syndrome, one of the things you want to try to give them on your exams is clindamycin.

Again, I don't know—I'm going off on this tangent of toxins—but toxins are very, very high-yield to know for Step 2 CK and Step 3. Again, they are not only relevant for Step 1, right?

But those toxins, right—they cause a lot of damage. Those exotoxins—exotoxins—exotoxins.

Remember, we tend to find exotoxins with gram-positive organisms, right? So those exotoxins cause problems. That's why if you're treating a person that has toxic shock syndrome, you want to use something that includes clindamycin, right?

Clindamycin is a 50S inhibitor. It's a protein synthesis inhibitor. Because it's a protein synthesis inhibitor—and a toxin is a protein—it'll reduce the production of those toxins. And that's going to help out the patient. OK?

What's another high-yield toxin thing to keep at the back of your mind for exams?

Another high-yield toxin integration—well, think of a person. Think of a person that—let's say they have redness and severe tenderness around their knee. And then you are told that man, over a 2–3 hour period, it's now starting to have bullous changes in the skin, and the redness has spread to the person's foot.

That person probably has necrotizing fasciitis—"neck fash." Again, many times neck fash is caused by organisms that elaborate a lot of toxins.

This is why part of the treatment regimen for necrotizing fasciitis is clindamycin. Again—50S inhibitor, protein synthesis inhibitor.

What's another toxin thing you can toss on Step 2 and Step 3? Well, think of a person that has watery diarrhea right after they've been treated for community-acquired pneumonia in the hospital.

Why would those people have watery diarrhea? Well, they have C. diff colitis. C. diff colitis.

Well, remember—how does C. diff get you in trouble? It gets you in trouble by releasing toxins, right? In fact, one of the ways we diagnose C. diff is by looking for the toxin in the stool.

Obviously, if a person has C. diff infection, you're going to treat them with oral vancomycin or oral fidaxomicin. Again, our friends at the NBME—they're not stupid. They know that all of you that have the job description "medical student" know about vancomycin.

But they know that many people—or at least an appreciable number of people—do not know about fidaxomicin. So please consider fidaxomicin on your exams, right?

Or what if they give you a question about a patient, and they tell you that this patient is a sex worker? And this sex worker patient has these painless lesions on the vaginal mucosa, right? And the patient is placed on oral antibiotic therapy—or IV antibiotic therapy.

OK, let's say IV antibiotic therapy. And then you're told that this patient, four hours after therapy was initiated, begins to have a rash, right? The patient begins to have reddening of the skin, becomes hypotensive.

Well, what are you thinking about?

I hope you're thinking about *Treponema pallidum*. You're thinking about syphilis and the Jarisch-Herxheimer reaction. The Jarisch-Herxheimer reaction, right?

So you are treating a person that has syphilis. You're giving a cell wall inhibitor, right? Penicillin.

Remember, penicillin is the treatment of choice for syphilis. And as you release those—as you use a cell wall inhibitor—the cell is literally exploding.

As the cell explodes, what do you think is going to be happening to all those things that it has within its intracellular environment?

It releases it into the bloodstream—again, kind of like a toxin.

Those things that are inside, like the cell soup of an organism, can trigger very powerful inflammation. And that can cause the person to have problems, right?

So keep that in mind for your exams.

What's another toxin they can test on your exam?

What if they give you a question about a person that's an immigrant from a foreign country, right? Immigrant. And they tell you that the person's vaccination history is unclear. And that this person, for the last four days, has been having a sore throat and has been having odynophagia, right?

And they tell you that the person is drooling. And I can almost promise you—on your exam—they will give you some labs, and they will even give you a throat exam, right? And you'll notice big, big, big-time swelling of the person's pharynx and things like that.

I can almost promise you—on your exam—one answer they're going to give you, they're going to give you epiglottitis, right? And they know that many people will rush headfirst to pick that answer.

Resist the temptation to pick that.

Look at the context that I'm giving here. Again, context really matters on the USMLEs. I'm giving the context of an immigrant. I'm giving the context of like, wow, you see this swelling of the pharynx and things like that.

What is this? This person has diphtheria. This person absolutely has what? Diphtheria.

Remember, diphtheria makes a toxin. That toxin—in fact, we call it the AB exotoxin. And how does this toxin work?

This toxin works by ribosylating elongation factor 2. OK? It causes ribosylation of elongation factor 2. When you ribosylate elongation factor 2, it's going to stop working.

When will you remember elongation factor 2 from? You probably remember elongation factor 2 from the process of translation, right? Of mRNA into a protein.

Again, you may be like, "Wow, Divine, you're drawing on so many things that I've learned from Step 1." Again—see, see, see—why do you think I'm going through the trouble of going through all these toxins and the mechanism of action of these toxins?

I'm not going through them because I like to hear myself speak. Again—see, you don't even have to believe what I'm saying. Just ask people that have taken Step 2 recently or people that have taken Step 3 recently. You're going to see that they ask these basic science questions where they ask about the mechanism of action of toxins.

In fact, I'm telling you this—that's actually a very, very high-yield thing to know for Step 2. And especially for Step 3.

Step 3 is one of those exams—don't get me wrong, Step 2 has a lot of basic science these days—but Step 3 has more basic science than you'd even expect, right?

Step 3 is almost like a Step 1 exam and a Step 2 exam rolled into one—with CCS cases thrown in for good measure and a lot more biostats than you're used to, right?

So please be careful about this. I know you may be like, "Divine, who cares about this stuff?" Well, you're going to care about it when you see it on the test. Actually do the studying and make sure you know these things, right?

So remember that the diphtheria toxin—it's an exotoxin. And what does it do? It causes ADP ribosylation of elongation factor 2. When you ribosylate elongation factor 2, you're going to shut down the synthesis of proteins because translation does not work as well as it should.

You're not going to be able to go from mRNA all the way to protein.

Are there other toxins that do this? Are there other toxins that cause ADP ribosylation? Absolutely, there are, right?

There are absolutely other toxins that can cause this ADP ribosylation. So we've talked about this in the context of the diphtheria toxin. But what are some other toxins that cause the same thing?

What are some other toxins that cause the same thing that you need to know for your exams?

Well, don't forget *Pseudomonas*. *Pseudomonas* has an A toxin that causes ADP ribosylation of elongation factor 2. OK?

So *Pseudomonas* also has a toxin that causes ADP ribosylation of elongation factor 2.

Again, please make sure you know this. Right?

Elongation is a step in translation. If you don't know this stuff—again, we wish you the best as you're preparing for your exams.

OK, what's another toxin that you should know for your tests? Right—think about the cholera toxin. Right? Remember, cholera has a toxin.

What does that cholera toxin do? Well, the cholera toxin causes you to secrete lots and lots and lots of chloride ions into the lumen of your GI tract.

As you secrete all those chloride ions, water is going to follow. And as water follows, you're going to have a secretory diarrhea.

Please do not lose sight of this on your test.

Let me actually tell you this: the cholera toxin basically activates adenylate cyclase, right? So as you activate adenylate cyclase, you're going to make a ton of cyclic AMP. And that's going to cause you to release a lot of chloride ions into the lumen of your GI tract.

Alright, so I think I've kind of hit toxins in a lot of the depth that I want to hit—at least these are a lot of the classic ones they love to go after on exams.

Let's say a few more things, and then we'll kind of wrap this up, right?

NSAID Use in Peptic Ulcer Disease

So what if they give you a question about a patient, and they tell you that this patient has osteoarthritis, right? But this patient also has a history of peptic ulcer disease, right?

So they say, “What is the most appropriate pharmacotherapy for this patient?”

I would really hope that you're picking an answer that talks about something like celecoxib, right?

You want to use a COX-2 inhibitor because this person has a history of peptic ulcer disease. You don’t want to give them a regular NSAID, because if you give them a regular NSAID, that can absolutely cause them to have an exacerbation of their peptic ulcer disease. They can bleed, right?

Because remember—how does a regular NSAID work?

A regular NSAID works by inhibiting COX-1 and COX-2, right? It’s a reversible inhibitor of COX-1 and COX-2. Remember, aspirin is an irreversible inhibitor of cyclooxygenase 1 and 2, right?

But the thing is, COX-1 works in the GI tract, right? COX-1 works in the GI tract. And you may ask, “Why is that such a big deal?”

Well, the problem is, if you inhibit COX-1 in the GI tract, you’re going to make less in the way of prostaglandins. And if you make less in the way of prostaglandins, then you're going to make a lot of acid in your GI tract—especially in your stomach.

As you make more acid, right—that’s going to mess up your stomach, and that’s going to cause you to have peptic ulcer disease.

So that’s why, if we can avoid something that targets COX-1, then we can help these people that have peptic ulcer disease, but still relieve their pain, still help them with inflammation—like in the setting of osteoarthritis, right?

So COX-2 is something that is not found in the GI tract, right? So if you want to get an NSAID-like effect but not target COX-1, use a COX-2 inhibitor like celecoxib. Use a COX-2 inhibitor like celecoxib.

Again, COX-2 inhibitors—they have very minimal gastrointestinal side effects.